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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,100	TANIGUCHI, NAOYUKI	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 20 December 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 are pending and under current examination.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claims 1-6 are objected to because of the following informalities: the claims are not grammatically correct throughout. For example, claim 1 recites "in which genome" in line 1 of the claim. This should read in which the genome. Further, for example, claim 3 recites "all alleles the genome", and this should read "all alleles in the genome". Applicants are requested to correct the various grammatical errors in the claims. The Examiner has not listed them in detail here, as there are too many to specifically recite.

Appropriate correction is required.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from
http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the

following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP § 2107 - 2107.02.

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility.

The claims are directed to a mouse or progenies thereof, in which the genome is modified so as to have decreased or deleted activity relating to modification of a sugar chain in which the 1-position of fucose is bound to the 6-position of N-acetylglucosamine in the reducing end through an a-bond in a complex N-glycoside-linking complex sugar chain. Further embodiments limit the enzyme to α1,6-fucosyltransferase. Specific embodiments are directed to the mouse, wherein the DNA is encoded by SEQ ID NO: 2; a DNA which hybridizes with the DNA comprising the nucleotide sequence represented by SEQ ID NO: 2 under stringent conditions and encodes a protein having α1,6-fucosyltransferase activity.

The specification discusses the structure of the gene of α1,6-fucosyltransferase, that the enzyme activity has been found in many organs, particularly in the brain and small intestines. The specification teaches various physiological roles, including retina formation, and blood coagulation. The specification states that increased α1,6-fucosyltransferase activity is also found in various disease states and cystic fibrosis. See pages 1-2. The specification teaches that a α1,6-fucosyltransferase hyperexpressing mouse was prepared and it exhibited an adiposis-like change in the liver and kidney. The specification teaches that the claimed mice and its progenies are used for "clarifying physiological roles of the α1,6-fucose modifying enzyme, and the relation of the to morbid states of disease." See pages 2-3, bridging sentence. The specification contemplates using the claimed mouse and/or its progenies for examination of 1) the physiological role of the enzyme in the process of development, 2) the physiological role of this enzyme during the processes after development and reaching the adult body and 3) the physiological role

of the enzyme in the adult body. The specification teaches that it is possible to observe a the physiological influence by a quantitative change of the α1,6-fucose modifying enzyme by comparing a normal, heterozygote and homozygous mouse. See page 20, #2 (1). Furthermore, the specification teaches that the mice can be used to clarify the relationship between the α1,6-fucose modifying enzyme and a particular disease state, and the mice can be used for the pharmacological evaluation of a substance to be tested out on the mouse and its progenies. See page 20, #2 (2). The specification further teaches various diseases that can be induced in the mice (pages 21-22). The specification teaches various contemplated uses of cells isolated from the mice, for pharmacological testing, inducing differentiation, to produce cells that would be used for such testing (pages 22-23).

In short, the specification contemplates 1) studying the physiological role of the α1,6-fucosyltransferase knockout mice; 2) using the knockout mice as a disease model; and 3) using the mice (or cells isolated therefrom) for drug screening assays. However, none of the contemplated utilities are a specific and substantial. The specification fails to provide a specific function for the α1,6-fucosyltransferase that is knocked out in the claimed mice. Although over expression of α1,6-fucosyltransferase has been implicated in various diseases, and it appears to be expressed in various tissues, there is no specific guidance as to its role in a particular disorder. The art supports that a specific role for α1,6-fucosyltransferase has yet to be established. For example, Yamaguchi *et al.* (**Glycobiology**, 10(6): 637-643, 2000) teach that overexpression of the α1,6-fucosyltransferase has been observed in a variety of cancers, in addition to liver cancers, it may play a putative role in other malignant disease. They state that, "Thus, the expression of this enzyme is likely to contribute to the malignant characteristics of cancer cells, and hence, an examination of the mechanism for the FUT expression is of importance in comprehending malignant potentials, such as invasive and

metastatic capabilities of the cells." They clearly teach that the physiological role and mechanism in which α1,6-fucosyltransferase contributes to any disease state is yet unknown. Post-filing art supports that the role of 1,6-fucosyltransferase is unknown, such as Martinez-Duncker *et al.* (Glycobiology,14(1): 13-25, 2004) teach that in humans, fucosyltransfereases and their expression are developmentally regulated. Particularly, the α1,6-fucosyltransferases a type II transmembrane protein (p. 13, col. 2, 2nd), and that various species of enzyme have been identified, including mouse, bovine, and porcine. They teach that there are 14 splice variants of the enzyme expressed in early human embryos (p. 14, 1st col, 1st ¶), but they provide no specific function for the enzyme.

Thus, at the time of filing, one of skill in the art would recognize that although the α1,6-fucosyltransferase gene had been identified, no particular role of the enzyme in a specific disease had been identified. The asserted utilities for the α1,6-fucosyltransferase gene-disrupted mice are not substantial. A substantial utility is one that defines a "real-world" use (see MPEP §2107.01, and Utility Guidelines, above). Thus, utilities that require or constitute further research to identify or reasonably confirm a "real world" context of use are not considered a substantial utility. In the instant case, the α1,6-fucosyltransferase gene has no determined physiological function, thus, in knocking out the endogenous mouse α1,6-fucosyltransferase gene to produce the instantly claimed knockout mice, one of skill in the art would not know how to use these mice in any of the asserted utilities, because basic research and further characterization would be required. Basic research, such as studying the properties of a claimed product itself or the mechanisms in which it is involved is not considered a substantial utility.

Furthermore, the use of the mice in determining function of that α1,6-fucosyltransferase gene is not sufficient for utility because the relationship between any phenotypes and gene function do not necessarily correlate.

Additional research would be required, based on the present disclosure, to determine what phenotypes (if any), since none are particularly disclosed, are related to α1,6-fucosyltransferase gene function. In the instant case, the physiological function of the α1,6-fucosyltransferase gene is not known in the art, nor disclosed in the specification at the time of filing and thus, the utility of the claimed invention is not apparent. As set forth in the utility guidelines, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient, absent a disclosure of what condition can be diagnosed. Similarly, a statement of therapeutic utility for an unspecified disease is non-specific, rendering the purported utility for the claimed mice to be non-specific. The usefulness of the mutant mice as models is not clear, without assessing that they specifically reflect a disease state, and this leaves the skilled artisan to speculate the uses of the knockout mouse. Additionally, utilizing the claimed mice to determine the physiological function of the α1,6-fucosyltransferase gene lacks a specific or substantial utility, because further research on the mouse is required to determine if any phenotypes are associated or correlated with the loss of the specific gene product, or due to some other phenomenon, such as the methodology used in making the mice. Under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention lacking in specific or substantial utilities.

The asserted utilities for the α1,6-fucosyltransferase gene-disrupted mice are not specific, because they are general utilities that are applicable to all knockout mice. All knockout mice can be used for disease models, to screen for agents or therapies. These utilities are not specific to the α1,6-fucosyltransferase gene disrupted mice because α1,6-fucosyltransferase functions in many pathways, and appears to be implicated in many diverse and varied diseases, the skilled artisan would not be able to elucidate the physiological role of α1,6-fucosyltransferase. Although the α1,6-

fucosyltransferase gene is expressed in various tissues, this fails to provide any guidance with regard to its particular function, or a correlation between its function (or lack thereof) to a particular disease or condition. Therefore, any utility of the claimed animals would require additional research, and further research to characterize an invention is not a specific and substantial utility. Although it is postulated that α1,6-fucosyltransferase overexpression is found to be present in various cancers, this fails to provide guidance for the lack of expression or reduction of expression of the gene. The specification provides no guidance as to the phenotype of the claimed mice, and thus, this lack of phenotype fails to provide a correlation to the function α1,6-fucosyltransferase gene, and therefore, is not specific to any disease or condition; thus, the artisan at the time of filing would not know how to use the mice in methods for treating an unspecified disease or condition associated with a disruption in the α1,6-fucosyltransferase gene.

The art at the time of filing, and Applicants' specification, fail to disclose a specific physiological function for the α1,6-fucosyltransferase gene, and thus, one of skill in the art could not use these mice to study an agent that has an effect on the α1,6-fucosyltransferase function. The art of record and specification fail to provide a correlation between a disruption or mutation in the α1,6-fucosyltransferase gene and a particular disease or condition, thus, one of skill in the art could not use these mice to treat or screen for agents to treat a disease or condition associated with the α1,6-fucosyltransferase gene. Because the physiological function of the α1,6-fucosyltransferase gene is unknown, a correlation between the disruption of the gene in a mouse and any resultant phenotypes is not evident, thus, one of skill in the art would need to determine if there is a correlation between the knockout of the gene and any non-disclosed, resultant phenotypes in the α1,6-fucosyltransferase gene-disrupted mice.

When determining whether an applicant has described the utility of invention, one has to determine whether the applicant has described a well-established utility. If not, has the applicant made any assertion of specific, substantial and credible utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for use. In contrast to general utility, a specific utility will be specific to the claimed subject matter. A substantial utility defines a real world utility of the invention and utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context use are not substantial utility (see utility guidelines, in Federal Register January 5, 2001, Volume 66, Number 5, Pages 1092-1099).

Absent the disclosure of the physiological function of the α1,6-fucosyltransferase gene, the invention is found to lack utility. While such use(s) may satisfy scientific curiosity as to the function of the α1,6-fucosyltransferase gene, they do not meet the utility under §101, since they are general uses that are applicable to the mutation of any gene in any cell or organism, and would require further experimentation of the invention itself. See *Brenner v. Manson*, 148 USPQ 689, 696 (US 1966).

To have a benefit, and therefore utility, more experimentation is required to characterize and identify the function of the α1,6-fucosyltransferase gene. For patentability, the claimed invention has to be in a useful form currently with specific benefit. The courts have stated in *Brenner V Manson* 148 USPQ 689,

> "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" (at 695) and "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion" at 696.

Thus, the claimed invention fails to have utility because it lacks

specific benefit in a currently available form and the requirement on the artisan to experiment on the claimed invention renders any patent issuing with the claimed invention the equivalent of a "hunting license." In essence, the uses for the claimed invention would amount to determining if the claimed invention had a use, and if so, identifying or defining its use. Because the claimed invention as a whole is not supported by a specific and substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Accordingly, in view of the lack of guidance or teachings in the specification or the art at the time of filing with regard to the specific function of the α1,6-fucosyltransferase gene, and for reasons set forth above, the skilled artisan would not find the asserted utilities of the gene disrupted α1,6-fucosyltransferase mouse, as encompassed by the claims, to be specific and substantial.

Enablement

Claims 1-6 are under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the

art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The invention is directed to a mouse or progenies thereof, in which the genome is modified so as to have decreased or deleted activity relating to modification of a sugar chain in which the 1-position of fucose is bound to the 6-position of N-acetylglucosamine in the reducing end through an α-bond in a complex N-glycoside-linking complex sugar chain. Further embodiments limit the enzyme to α1,6-fucosyltransferase. Specific embodiments are directed to the mouse, wherein the DNA is encoded by SEQ ID NO: 2; a DNA which hybridizes with the DNA comprising the nucleotide sequence represented by SEQ ID NO: 2 under stringent conditions and encodes a protein having α1,6-fucosyltransferase activity.

Breadth of the claims. The claims broadly encompass any enzyme that relates to the modification of a sugar chain in which the 1-position of fucose is bound to the 6-position of the N-acetylglucosamine in the reducing end through an α-bond in a complex N-glycoside-linking complex sugar chain. The claims broadly encompass heterozygous and homozygous mice.

Claims 5-6 are so broad as to encompass (1) any nucleic acid which hybridizes under any conditions to the polynucleotide of SEQ ID NO: 2, (2) any protein with α1,6-fucosyltransferase activity that has any number of deletions, insertions, or additions; and (3) any protein having α1,6-

fucosyltransferase activity, wherein said protein has an amino acid sequence 80% or more homologous to SEQ ID NO:1,

The enablement provided is not commensurate in scope with the claims due to the extremely large number of nucleic acids of unknown structure or function recited in the claims as well as the lack of information regarding the structural elements in the polynucleotide of SEQ ID NO: 2 or the polypeptide of SEQ ID NO: 1 which are required and those which can be modified to obtain the extremely large number of variants claimed encoding a protein having the α1,6-fucosyltransferase activity of the polypeptide of SEQ ID NO: 1. Furthermore, since there is either no structural or functional limitation associated with the claimed genus of nucleic acids, and the specification provides no correlation between the structures disclosed and fucosyltransferase activity, the genus encompasses polynucleotides which the skilled artisan would not know how to make and/or use as their structure or function is unknown. In the instant case, the specification discloses the polynucleotide of SEQ ID NO: 2 (α1,6-fucosyltransferase).

Guidance of the Specification/The Existence of Working Examples. The specification teaches the sequence of α1,6-fucosyltransferase but no information or guidance as to which amino acid residues in the polypeptide of SEQ ID NO: 2 can be modified and which ones are to be conserved to create a variant displaying the same activity as that of the polypeptide of SEQ ID NO: 1. Similarly, there is no information or guidance as to which nucleotides in the polynucleotide of SEQ ID NO:2 can be modified and which ones are to be conserved to create a variant which encodes an α1,6-fucosyltransferase.

'The specification teaches the production of homozygous α1,6-fucosyltransferase knockout mice. They teach producing a targeting vector (pages 25-26), injection of the targeting vector into mouse ES cells and selection of positive clones (pages 29-30), verification of homologous recombination by genomic Southern blotting (pages 31-32); the production of

chimeric mice by injection of the positive ES cell clones into mouse blastocysts (page 33); the selection of germ line chimeras, which were then bred to produce heterozygous FUT8 knockout mice (page 33, #2); the mating of heterozygous mice to produce homozygous α1,6-fucosyltransferase knockout mice (page 34). The specification further teaches that the α1,6-fucosyltransferase knockout mice did not express α1,6-fucosyltransferase (Example 2).

State of the Art/Predictability of the Art. The specification provides no guidance with regard to the phenotype of the claimed mice, thus, one of skill in the art, would not know how to use these mice. To this end, the specification does not provide guidance for any particular phenotype for the claimed transgenic mice, other than the anticipated lack of expression of the knocked out gene.

Although one of skill in the art would know how to produce a knockout mouse, one of skill could not rely upon the state of the art to predict the resultant phenotype of the mouse. Because the physiological role of the α1,6-fucosyltransferase gene has not been elucidated (see discussion above, under §101), one of skill in the art could not predict the phenotype of the α1,6-fucosyltransferase gene-disrupted mice. For example, Leonard [**Immunological Reviews**, (148): 98-113 (1995)] disclose mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths [**Microscopy Research and Technique**, 41:344-358 (1998)] taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Additionally, Holschneider *et al.* [**Int J. Devl. Neuroscience**

18:615-618, 2000] support this unpredictability, stating that the, "knocking out or insertion of a single gene may result in no phenotypic change. This may be the case, in particular, if there exist gene redundancy mechanisms whose presence may prevent abnormal phenotypes from becoming masked. Conversely, single genes are often essential in a number of different behaviors and physiologic processes. Hence, ablation of an individual gene may prove so drastic as to be lethal, or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interactions of the various new physiologic changes or behaviors." [See p. 615, col. 1-2]. Holschneider *et al.* discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory systems which may be activated to mask the resulting phenotype, these compensatory changes may be due to the differential expression of another gene, which may be regulated by the downstream product of the ablated gene, as well as the variability in phenotypic characterization due to particular mouse strains [see p. 616, 1st column].

Furthermore, Pearson (**Nature**, 415:8-9 (3 January 2002)) review the state of the art of knockout mice with regard to their resultant phenotypes, and state that, "In many cases, a mutant mouse does not show any obvious characteristics – or phenotype. In others, the phenotype disappears when the disabled gene is crossed into a different strain of mouse. Indeed, clear and consistent phenotypes now seem to the exception rather than the rule." See page 8, 1st column, 4th ¶. Pearson states that the phenotype of a knockout mouse is dependent on various factors, including the strain of mouse, the overlapping of gene function to mask a particular phenotype, and the particular environment that the mouse is in, can all affect the resultant phenotype.

The specification has provided no specific guidance for the phenotype of the α1,6-fucosyltransferase gene-disrupted mice and one of skill in the art

would not be able to rely upon the art at the time of filing, because the art recognized that knockout of a particular gene fails to result in a predictable phenotype. Given that specific phenotypic alterations cannot be predictably achieved by merely knocking out of a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

The nucleotide sequence of the coding region of a polynucleotide encoding a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any nucleic acid encoding a polypeptide having the same biological function as that of the polypeptide of SEQ ID NO: 1. In addition, the art does not provide any teaching or guidance as to (1) which nucleotides in the polynucleotide of SEQ ID NO: 2 can be modified and which ones are conserved such that one of skill in the art can make variants as recited encoding polypeptides with the same biological activity as that of the polypeptide of SEQ ID NO: 2, (1) which segments of the polypeptide of SEQ ID NO: 2, or the polynucleotide of SEQ ID NO: 2, are essential for activity, and (3) the general tolerance of the breadth of enzymes (that modify a sugar chain in which the 1-position of fucose is bound to the 6-position of N-acteylglucosamine in the reducing end through an α-bond in a complex N-glycoside-linked complex sugar chain), to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity.

For example, the conservative replacement of a single lysine residue at position 118 of acidic fibroblastic growth factor by a glutamic acid, led to the substantial loss of heparin binding, receptor binding and the biological activity of the protein (see Burgess *et al.*, J. of Cell Bio., 111: 2129-2138 (1990)). In transforming growth factor alpha, the replacement of aspartic acid at position 47 with alanine or asparagines did not affect the biological activity, however, the replacement of serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar *et al.*, Mol. & Cell. Bio., 8: 1247-1252 (1998)). Thus, these references demonstrate that even a single amino acid substitution, or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity and characteristic of a protein. Furthermore, as the specification fails to teach what deletions/insertions or substitutions of the disclosed sequence would be tolerated in order to allow the α1,6-fucosyltransferase to function as claimed. While it is known that many amino acid substitutions are possible, in any given protein, the position within the protein's sequence, where such an amino acid substation(s) can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can only tolerate conservative substitutions, or no substitutions at all. Residues that are directly involved in protein functions, such as binding, will certainly be among the most conserved There is no specific guidance provided by the specification with regard to the particular domains that are essential to the function of the α1,6-fucosyltransferaseprotein. Therefore, reasonable correlation must exist between the scope of the claims and scope of enablement set forth and it cannot be predicted from the disclosure how to make and use the nucleic acid(s) that encode peptide variants of α1,6-fucosyltransferase.

The Amount of Experimentation Necessary. Thus, the claims are not enabled because the skilled artisan, at the time of filing, would not know how to use the claimed mice. Because the physiological function of α1,6-fucosyltransferase is unknown, and further, with regard to a lack of correlation between the knockout of this gene and particular disease, one of skill in the art could not readily rely upon the state of the art with regard to a correlation between a disruption in an endogenous mouse α1,6-fucosyltransferase gene and any resultant phenotype exhibited by the mouse.

Furthermore, while methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all polynucleotides encoding polypeptides having α1,6-fucosyltransferase activity. In the absence of (1) a rational and predictable scheme for modifying any nucleotide in the nucleic acid of SEQ ID NO: 2 such that the resulting variant would encode a protein which retains α1,6-fucosyltransferase activity, and/or (2) a correlation between structure and α1,6-fucosyltransferase activity, one of skill in the art would have to test an essentially infinite number of polynucleotides to determine which ones encode proteins having α1,6-fucosyltransferase activity.

While enzymatic assays are well known in the art, and the skilled artisan can produce variants of the polynucleotide of SEQ ID NO: 2 or the polypeptide of SEQ ID NO: 1, having the recited structural characteristics using well-known and widely used techniques in the art, the amount of experimentation required is not routine due to the fact that the number of species encompassed by the claims is extremely large. Therefore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of

species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Accordingly, in view of the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, the lack of teachings or guidance provided by the specification with regard to an enabled use for mice comprising a disruption in an endogenous α1,6-fucosyltransferase gene, the lack of teachings or guidance with regard to the disclosed specific physiological function of the α1,6-fucosyltransferase gene, the lack of teachings or guidance provided by the specification to overcome the art-recognized unpredictability of disruption of a particular gene and the resulting phenotype, and correlation between a disruption in the α1,6-fucosyltransferase gene and a particular disease or condition, and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Written Description

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117.

The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

Claims 1-4 are directed to an enzyme that relates to the modification of a sugar chain in which the 1-position of fucose is bound to the 6-position of N-acteylglucosamine in the reducing end through an α-bond in a complex N-glycoside-linked complex sugar chain. The specification does not provide a written description for the genus of enzymes encompassed by these claims, the specification provides a single species, α1,6-fucosyltransferase, which acts in this manner. The specification provides no guidance or description as to which enzymes would be encompassed in this genus, and would have the activity required of the enzyme. Furthermore, the claims state that the enzyme relates to the modification of the sugar chain. The specification only teaches that α1,6-fucosyltransferase transfers a fucosyl residue to the 6-position of N-acetylglucosamine. The term "modification" encompasses either the addition (transfer) or removal of a residue. The specification does not describe enzymes that removal residues and modify the sugar chain, with the activity required by the claims.

Claim 5, part (b) is directed to a genus of nucleic acids which hybridize under any conditions to the polynucleotide of SEQ ID NO: 2 and encode proteins having α1,6-fucosyltransferase activity. Claim 6 is directed to a mouse or its progenies, wherein the α1,6-fucosyltransferase is a protein which comprises an amino acid sequence in which at least one amino acid in amino acid sequence represented by SEQ ID NO: 1 is *deleted, substituted, inserted and/or added* and has α1,6-fucosyltransferase activity. The specification does not provide a description for the genus of nucleic acids with a structural limitation, since the claim as written allows for any number of changes to SEQ ID NO: 1. As such, any protein having α1,6-fucosyltransferase activity can be a protein having α1,6-fucosyltransferase

activity and comprising an amino acid sequence derived from SEQ ID NO: 1 by deletion, substitution, and/or addition of one or more amino acids.

Claim 6, part (c) is directed to a genus of proteins with α1,6-fucosyltransferase function wherein said proteins have α1,6-fucosyltransferase activity and wherein said polypeptide is at least 80% sequence homologous to the polypeptide of SEQ ID NO: 1.

As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, the claims encompass a genus of nucleic acids lacking either a structural or a functional limitation. While the specification in the instant application discloses the structure of a single species, α1,6-fucosyltransferase, the specification fails to describe any additional species by any relevant, identifying characteristics or properties other than by functionality (i.e., modification activity). In addition, while the claims require genes encoding proteins having α1,6-fucosyltransferase activity, no description has been provided as to the structural features of non-coding regions of any gene encoding the α1,6-fucosyltransferase enzyme, such as the regulatory elements and untranslated regions, nor there is a correlation

between the disclosed function and the structure of non-coding regions of any gene encoding a α1,6-fucosyltransferase. Moreover, there is no disclosure of a correlation between the structure of the polynucleotide of SEQ ID NO: 2 and the structural features of those regions in a gene encoding α1,6-fucosyltransferase which are non-coding.

The claims encompass an extremely large genus of nucleic acids which are structurally or functionally unrelated. A sufficient written description of a genus of nucleic acids may be achieved by a recitation of a representative number of nucleic acids defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, either (1) there is no structural feature which is representative of all the members of the genus of nucleic acids recited in the claims, or (2) the structural features recited/interpreted, such as "80% sequence homology to SEQ ID NO: 1", "DNA hybridizing under any conditions to the polynucleotide of SEQ ID NO: 2", do not constitute a substantial portion of the genus as the remainder of any nucleic acid encoding/comprising said structural elements is completely undefined and the specification does not define the remaining structural features for members of the genus to be selected.

While one could argue that SEQ ID NO: 2 is representative of all the members of the genus of nucleic acids claimed, or that the polypeptide of SEQ ID NO: 1 is representative of all the members of the genus of proteins encoded by the genus of nucleic acids claimed, such that the recited genus is adequately described by the disclosure of the structure of the polynucleotide of SEQ ID NO: 2, or the polypeptide of SEQ ID NO: 1, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and

completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with claimed activity has been provided, one cannot reasonably conclude that the structures disclosed are representative of all nucleic acids encoding α1,6-fucosyltransferase or nucleic acids encoding proteins of any function as claimed.

Due to the fact that the specification only discloses a single species of the genus of α1,6-fucosyltransferases recited, and a single species of the genus of nucleic acids encoding α1,6-fucosyltransferases claimed (SEQ ID NO: 2), as well as the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. The claims lack a written description, because the specification provides no guidance with regard to 1)

deletions/insertions or substitutions in the α1,6-fucosyltransferase sequences that result in peptides with the claimed functions or 2) DNA sequences that hybridize to α1,6-fucosyltransferase DNA, under stringent conditions, with the claimed properties. Absent factual evidence, a nucleic acid having a percentage sequence similarity of less than 100% would not be deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of a similar, known biomolecule. It known for nucleic acids, as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Even in polypeptide families, individual members can have distinct, and even opposite biological activities.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by any member of the genus of enzymes that modify (in any way) sugar chains in which the 1-position of fucose is bound to the 6-position of N-acteylglucosamine in the reducing end through an α-bond in a complex N-glycoside-linked complex sugar chain, DNA that hybridizes (under any condition) to SEQ ID NO: 2 that encodes a protein having α1,6-fucosyltransferase activity, proteins wherein the amino acid sequence has at least one deletion, insertion, or addition and have α1,6-fucosyltransferase, or proteins that have an amino acid sequence of 80% or more homology with SEQ ID NO: 1 and have α1,6-fucosyltransferase activity.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were

found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 are unclear. They recite that the enzyme "relates to the modification of a sugar chain". It is unclear what the metes and bounds of this phrase are, and particularly, how the enzyme relates to modification. If the enzyme modifies a sugar chain, then the claim should be amended to clearly reflect this. Appropriate correction is requested.

Claim 2 is confusing. The claim recites that "genomic gene" of the enzyme is knocked out. The enzyme does not have a genome, so it is unclear how a gene could be knocked out from an enzyme. Furthermore, the metes and bounds of "genomic gene" are unclear. The genome comprises all the genes of an organism. Thus, what "genomic gene" encompasses is unclear, or redundant. Appropriate correction is requested.

Claim 3 is unclear. The claim recites that "all alleles on the genome of the enzyme" in lines 1-2 of the claim. Alleles are not "on" a genome, and further, an enzyme does not have a genome. It is further confusing because this claim implies there could be more than two alleles, because it recites "all alleles". Appropriate correction is requested.

The term "stringent conditions" in claim 5 is a relative term which renders the claim indefinite. The term "stringent conditions" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanda *et al.* (**WO/0231140**, Publication date 4/18/02) (specifically, pages 5, 6, 8, 9, 20, 26, 27 only) when taken with Capecchi [**U.S. Pat. No. 5,464,764**, November 7, 1995], as evidenced by alignment of SEQ ID NO: 2 of the instant application with SEQ ID NO: 1 of the Kanda reference. The Examiner has only provided the appropriate, translated pages that are specifically referred to in this rejection, and not the entire '140 document).

Kanda teach a CHO cell, wherein the activity of an enzyme relating to the modification of a sugar chain in which the 1-position of fucose is bound to the 6-position of N-acteylglucosamine in the reducing end through an α-bond in a complex N-glycoside-linked complex sugar chain is decreased or deleted (page 5, lines 8-10). They specifically teach that the enzyme is a α1,6-fucosyltransferase (p. 6, line 8), and teach that the α1,6-fucosyltransferase can be a protein selected from SEQ ID NO: 23, a protein that comprises an amino acid sequence in which at least one amino acid is deleted, substituted, inserted and/or added, and has α1,6-fucosyltransferase activity, or a protein

with at least 80% activity with the amino acid sequence represented by SEQ ID NO: 23, and has α1,6-fucosyltransferase activity (p. 6, lines 15-24); They teach methods of decreasing or deleting the enzyme activity, such as using gene disruption techniques (p. 6, lines 25-34). They specifically contemplate producing transgenic non-human animals or progenies there of, wherein the α1,6-fucosyltransferase activity is decreased or deleted (pages 8-9, bridging sentence, and p. 9, lines 36-49), using a DNA that comprises SEQ ID NO: 1, and specifically contemplate that the transgenic animal is a mouse (p. 9, line 53). The Examiner provides the evidence of sequence alignment of SEQ ID NO: 1 of Kanda is 100% similar to SEQ ID NO:2 of the instant application. Kanda teach how to disrupt the α1,6-fucosyltransferase gene by homologous recombination (p. 20). They further discuss specific methods to produce the α1,6-fucosyltransferase knockout animal (pages 26-27)

Kanda do not teach the actual production of the knockout mice, however, this technology was well-known prior to the time of the claimed invention. Capecchi teach a vector to be used to produce knockout mice. Particularly, that the vector has a first and second homologous DNA sequence, and a positive selection marker between the two homologous sequences. See Figure 1. Furthermore, they teach various markers that can be used in these vectors. See Table I, col. 7-8. They teach that these vectors can then be used to produce transgenic animals, wherein ES cells are the target cells (see col. 15, lines 59-67), wherein the vector can then be introduced into the ES cells by electroporation or microinjection. These transformed ES cells can then be combined with a blastocysts and then grown and contribute to the germ line of the resulting chimeric animal. Col. 16, lines 1-10. They teach that cell lines from the animals can then be used to characterize gene function, or be used in assays. See col. 12-13, bridging ¶. Cappechi clearly show that these vectors and methods can be used to determine the biological function of any known gene of interest.

Accordingly, given the combined teachings of Kanda and Capecchi, it would have been obvious for one of ordinary skill in the art to use the methods of producing knockout mice, taught by Capecchi, and the sequence provided by Kanda to arrive at the claimed invention, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make these mice, as suggested by Capecchi, study the physiological role of the gene. Note: absent any phenotypic requirement in the claims, it would be obvious to produce the claimed mice.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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